FORM PTO-1390 (REV 10-95) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. §371	SCH 1706
	U.S. APPLICATION NO (If known, see 37 CFR §1.5) 09/787396

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/07089	16 SEPTEMBER 1999	18 SEPTEMBER 1998

TITLE OF INVENTION

BENZOXAZINE AND BENZOTHIAZINE DERIVATIVES AND THEIR USE IN MEDICINES

APPLICANT(S) FOR DO/EO/US

HOLSCHER, Peter, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ■ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. §371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. §371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. §371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. §371(b) and PCT Articles 22 and 39(1).
4. ■ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ■ A copy of the International Application as filed (35 U.S.C. §371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ■ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ■ A translation of the International Application into English (35 U.S.C. §371(c)(2)).
7. ■ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. §371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ■ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. §371(c)(3)).
9. ■ An oath or declaration of the inventor(s) (35 U.S.C. §371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. §371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 C.F.R. §§1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. §§3.28 and 3.31 is included.
13. ■ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/787396	PCT/EP99/07089	SCH 1706

17. ☒ The following fees are submitted:

CALCULATIONS PTO USE ONLY

BASIC NATIONAL FEE (37 CFR §1.492 (a) (1) - (5)):

Search Report has been prepared by the EPO or JPO	$860.00
International preliminary examination fee paid to USPTO (37 CFR §1.482)	$690.00
No international preliminary examination fee paid to USPTO (37 CFR §1.482) but international search fee paid to USPTO (37 CFR §1.445(a)(2))	$710.00
Neither international preliminary examination fee (37 CFR §1.482) nor international search fee (37 CFR §1.445(a)(2)) paid to USPTO	$1000.00
International preliminary examination fee paid to USPTO (37 CFR §1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)	$100.00

ENTER APPROPRIATE BASIC FEE AMOUNT = $860.00

Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(e)).

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	15 - 20 =	0	x $ 18.00	$0.00
Independent claims	2 - 3 =	0	x $ 80.00	$0.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $ 270.00	

TOTAL OF ABOVE CALCULATIONS = $860.00

Reduction of 1/2 for filing by small entity, if applicable. A Verified Small Entity Statement must also be filed (Note 37 C.F.R. §§1.9, 1.27, 1.28).

SUBTOTAL = $860.00

Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 C.F.R. §1.492(f)).

TOTAL NATIONAL FEE = $860.00

Fee for recording the enclosed assignment (37 C.F.R. §1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 C.F.R. §§3.28, 3.31). $40.00 per property.

TOTAL FEES ENCLOSED = $860.00

Amount to be refunded:

charged:

a. ■ A check in the amount of $860.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 13-3402 in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ■ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-3402. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 C.F.R. §§1.494 or 1.495 has not been met, a petition to revive (37 C.F.R. §1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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23599
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Filed: 19 MARCH 2001

AJZ; kms

SIGNATURE

Anthony J. Zelano
NAME

27,969
REGISTRATION NUMBER

IN THE UNITED STATES DESIGNATED/ELECTED OFFICE

International Application No.	:	PCT/EP99/07089
International Filing Date	:	16 SEPTEMBER 1999
Priority Date(s) Claimed	:	18 SEPTEMBER 1998
Applicant(s) (DO/EO/US)	:	HOLSCHER, Peter, et al.

Title: BENZOXAZINE AND BENZOTHIAZINE DERIVATIVES AND THEIR USE IN MEDICINES

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

SIR:

Prior to calculating the national fee, and prior to examination in the National Phase of the above-identified International application, please amend as follows:

IN THE CLAIMS:

3. (Amended) Compounds according to claim 1, in which R^6 is C_{1-6} alkyl.

4. (Amended) Compounds according to claim 1, in which R^4 is hydrogen.

5. (Amended) Compounds according to claim 1, in which X is oxygen or sulfur.

6. (Amended) Compounds according to claim 1, in which R^1 and R^2 together with two adjacent carbon atoms mean a 3- to 8-membered, preferably 5- to 6-membered ring, which is substituted with

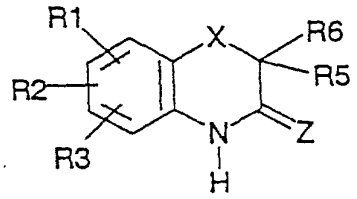
$-(CHR^9)_r-NR^7-A-NR^8B$.

8. (Amended) Compounds according to claim 1, in which A means a straight-chain or branched C_{1-6} alkylene or $-(CH_2)_p-Q-(CH_2)_q-$, and p and q mean 1-4.

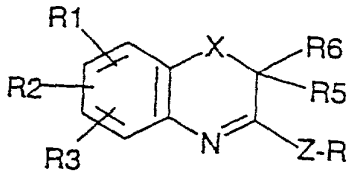
11. (Amended) Pharmaceutical agent that contains a compound according to claim 1 and one or more pharmaceutically common vehicles or adjuvants.

12. (Amended) Use of a compound according to claim 1 for the production of a pharmaceutical agent for treating a disease that is triggered by NOS.

14. (Amended) Process for the production of a compound of formula I according to claim 1, characterized in that a compound of formula II or its salt



IIa or



IIb

in which

R^1, R^2, R^3, R^5, R^6 and X have the above-mentioned meaning, Z is oxygen or sulfur and R means C_{1-6} alkyl, is reacted with ammonia or primary amines, whereby existing amino groups are optionally intermediately protected and optionally then acylated, the isomers are separated or the salts are formed.

REMARKS

The purpose of this Preliminary Amendment is to eliminate multiple dependent claims in order to avoid the additional fee. Applicants reserve the right to reintroduce claims to canceled combined subject matter.

Respectfully submitted,

____

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AJZ:jmm

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 3-6, 8, 11-12 and 14 have been amended as follows:

3. (Amended) Compounds according to ~~claims 1-2~~ claim 1, in which R^6 is C_{1-6} alkyl.

4. (Amended) Compounds according to ~~claims 1-3~~ claim 1, in which R^4 is hydrogen.

5. (Amended) Compounds according to ~~claims 1-4~~ claim 1, in which X is oxygen or sulfur.

6. (Amended) Compounds according to ~~claims 1-5~~ claim 1, in which R^1 and R^2 together with two adjacent carbon atoms mean a 3- to 8-membered, preferably 5- to 6-membered ring, which is substituted with

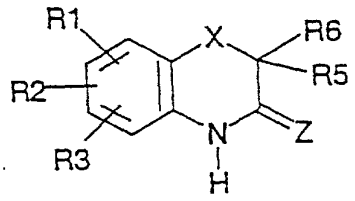
$-(CHR^9)_r-NR^7-A-NR^8B$.

8. (Amended) Compounds according to ~~claims 1-7~~ claim 1, in which A means a straight-chain or branched C_{1-6} alkylene or $-(CH_2)_p-Q-(CH_2)_q-$, and p and q mean 1-4.

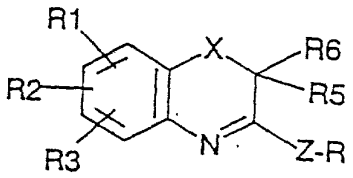
11. (Amended) Pharmaceutical agent that contains a compound according to ~~claims 1-10~~ claim 1 and one or more pharmaceutically common vehicles or adjuvants.

12. (Amended) Use of a compound according to ~~claims 1-10~~ claim 1 for the production of a pharmaceutical agent for treating a disease that is triggered by NOS.

14. (Amended) Process for the production of a compound of formula I according to ~~claims 1-3~~ claim 1, characterized in that a compound of formula II or its salt



IIa or



IIb

in which

R^1, R^2, R^3, R^5, R^6 and X have the above-mentioned meaning, Z is oxygen or sulfur and R means C_{1-6} alkyl, is reacted with ammonia or primary amines, whereby existing amino groups are optionally intermediately protected and optionally then acylated, the isomers are separated or the salts are formed.

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INTERNATIONAL APPLICATION PUBLISHED ACCORDING TO THE PATENT COOPERATION TREATY (PCT)

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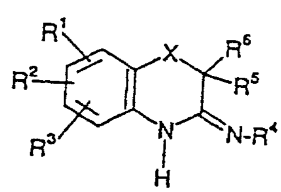
Published:

With international search report.

Before expiration of the time limit allowed for amendment of the claims. It will be republished if amendments are made.

(54) **Title: BENZOXAZINE AND BENZOTHIAZINE DERIVATIVES AND THEIR USE IN PHARMACEUTICAL AGENTS**



(I)

(57) **Abstract**

Compounds of Formula (I), their tautomeric and isomeric forms and salts, as well as the process for their production and their use in pharmaceutical agents are described.

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Benzoxazine and Benzothiazine Derivatives and their Use in Pharmaceutical Agents

The invention relates to benzoxazine and benzothiazine derivatives, the process for their production and their use in pharmaceutical agents.

In human cells, there exist at least 3 forms of nitrogen monoxide synthases, which convert arginine into nitrogen monoxide (NO) and citrulline. Two constitutive NO-synthases (NOS) were identified that are present as calcium/calmodulin-dependent enzymes in the brain (ncNOS or NOS 1) or in the endothelium (ecNOS or NOS 3). Another isoform is the inducible NOS (iNOS or NOS 2), which is a virtually Ca^{++}-independent enzyme and is induced after activation of different cells by endotoxin or other substances.

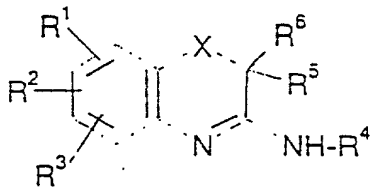
NOS-inhibitors and especially selective inhibitors of NOS 1, NOS 2 or NOS 3 are therefore suitable for treatment of different diseases, which are induced or aggravated by pathological concentrations of NO in cells. A number of reviews provide information on the action and inhibitors of NO-synthases. Mentioned are, for example: Drugs 1998, 1, 321 or Current Pharmac. Design 1997, 3, 447.

As NOS-inhibitors, different compounds are known. For example, arginine derivatives, aminopyridines, cyclic amidine derivatives, phenylimidazoles, etc. are described. It is not

known from any publication that 1,4-benzoxazines and 1,4-benzothiazines inhibit nitrogen monoxide synthases in a potent and selective manner.

It has now been found that the heterocycles that are substituted according to the invention, compared to known compounds, can be used especially advantageously as pharmaceutical agents.

The invention relates to the compounds of formula I, their tautomeric and isomeric forms and salts



(I)

in which

X is O, SO_m or Se,

R^1 is $-(CHR^9)_n-NR^7-A-NR^8-B$,

R^2 is hydrogen or

R^1 and R^2 together with two adjacent carbon atoms form a 5-, 6-, 7- or 8-membered ring, which is monocyclic or bicyclic, saturated or unsaturated and in which 1 or 2 CH_2 groups can be replaced by oxygen or carbonyl, and which is substituted with $(CHR^9)_r-NR^7-A-NR^8-B$, and can be substituted with C_{1-4} alkyl,

R^3 means hydrogen, halogen, NO_2, cyano, CF_3, $-OCF_3$,

$-S-R^9$, $-O-R^9$, C_{3-7} cycloalkyl, $-NR^9-C(=NR^{10})-R^{11}$, $-NH-CS-NR^{12}R^{13}$, $NH-CO-NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-CO-NR^{12}R^{13}$, $-CO-R^{14}$, $NR^{15}R^{16}$, C_{6-10} aryl, which optionally is substituted with halogen, cyano, C_{1-4} alkyl, $-S-R^9$, or $-O-R^9$,

5- or 6-membered heteroaryl with 1 to 4 oxygen, sulfur or nitrogen atoms,

C_{1-6} alkyl, which optionally is substituted with halogen, $-OR^9$, $-SR^9$, $-NR^{12}R^{13}$, $=NR^{12}$, $=NOC_{1-6}$ alkyl, =N-NH aryl, phenyl, C_{3-7} cycloalkyl or 5- or 6-membered heteroaryl,

C_{2-6} alkenyl, which optionally is substituted with halogen, $CONH_2$, C≡N or phenyl,

C_{2-6} alkinyl, which optionally is substituted with halogen, $CONH_2$, C≡N or phenyl,

R^4 means hydrogen or acyl,

R^5 and R^6, independently of one another, mean hydrogen, C_{3-7} cycloalkyl, phenyl, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl radicals, which can be substituted in each case with halogen, OH, $O-C_{1-6}$ alkyl, SH, $S-C_{1-6}$ alkyl, $NR^{15}R^{16}$, 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, phenyl or C_{3-7} cycloalkyl,

R^7 means hydrogen, C_{1-6} alkyl, which can be substituted with phenyl, $COOC_{1-6}$ alkyl or $CO-C_{1-6}$ alkyl,

R^8 means hydrogen, C_{1-6} alkyl, which can be substituted with phenyl, $COOC_{1-6}$ alkyl or COC_{1-6} alkyl,

A means straight-chain or branched C_{1-6} alkylene, straight-chain or branched C_{1-6} alkenylene or $-(CH_2)_p-Q-(CH_2)_q-$,

B means hydrogen or $-(CH_2)_p-U$,

Q means C_{3-7} cycloalkyl, indanyl, 5-, 6- or 7-membered saturated heterocycloalkyl with 1-2 N, O or S atoms, C_6-C_{10} aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which can be anellated with benzene,

U means hydrogen, C_{1-6} alkyl optionally substituted with halogen, C_{3-7} cycloalkyl, indanyl, C_{7-10} bicycloalkyl, C_{6-10} aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which can be anellated with benzene, whereby the aryl and heteroaryl radical can be substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, NO_2, NH_2, $N(C_{1-4}$ alkyl$)_2$, cyano, $CONH_2$, $-O-CH_2-O-$, $-O-(CH_2)_2-O-$, SO_2NH_2, OH, phenoxy or $COOC_{1-4}$ alkyl,

or

R^8 and B together with the nitrogen atom form a 5- to 7-membered saturated heterocycle, which can contain another oxygen, nitrogen or sulfur atom and can be substituted with C_{1-4} alkyl, phenyl, benzyl or benzoyl or form an unsaturated 5-membered heterocycle, which can contain 1-3 N atoms and can be substituted with phenyl, C_{1-4} alkyl or halogen, or

R^7 and A together with the nitrogen atom form a 5- to 7-membered saturated heterocycle, which can contain another oxygen, nitrogen or sulfur atom or forms an

unsaturated 5-membered heterocycle, which can contain 1-3 N atoms,

m means 0, 1 or 2,

n and r mean 0, 1 to 6,

p and q mean 0 to 6,

R^9 and R^{10} mean hydrogen or C_{1-6} alkyl,

R^{11} means C_{1-6} alkyl, $-NH_2$, $-NH-CH_3$, -NH-CN, C_{6-10} aryl optionally substituted with halogen, C_{1-4} alkyl or CF_3, or 5- or 6-membered heteroaryl with 1 to 4 nitrogen, sulfur or oxygen atoms that is optionally substituted with halogen, C_{1-4} alkyl or CF_3,

R^{12} and R^{13} mean hydrogen, C_{1-6} alkyl, phenyl optionally substituted with halogen or C_{1-4} alkyl, benzyl optionally substituted with halogen or C_{1-4} alkyl or C_{3-7} cycloalkyl,

R^{14} means hydrogen, hydroxy, C_{1-6} alkoxy, phenyl, C_{1-6} alkyl optionally substituted with CO_2H, CO_2C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy, halogen, $NR^{15}R^{16}$, $CONR^{12}R^{13}$, or phenyl, or C_{2-6} alkenyl optionally substituted with phenyl, cyano, $CONR^{12}R^{13}$ or CO_2C_{1-4} alkyl,

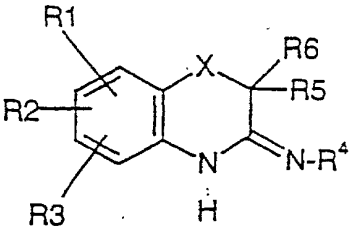
R^{15} and R^{16} mean hydrogen, C_{1-6} alkyl, phenyl or benzyl or

R^{15} and R^{16} together with the nitrogen atom form a saturated 5-, 6-, or 7-membered ring, which can contain another nitrogen, oxygen or sulfur atom and can be substituted with C_{1-4} alkyl, phenyl, benzyl or benzoyl,

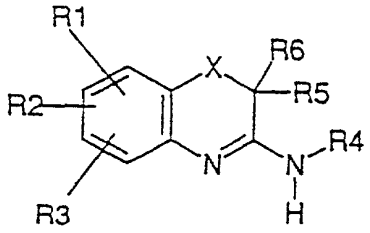
whereby

if X = 0, R^6 means methyl and R^2, R^3, R^4 and R^5 mean hydrogen, R^1 is not 6-((4-aminobenzyl)aminomethyl), 6-((4-dimethylaminobenzyl)aminomethyl), 6-((4-aminobenzyl)(tert-butyloxycarbonyl)aminomethyl), 6-((4-dimethylaminobenzyl)(tert-butyloxycarbonyl)aminomethyl).

The compounds of the formula can be present as tautomers, stereoisomers or geometric isomers. The invention also comprises all possible isomers, such as E- and Z-isomers, S- and R-enantiomers, diastereomers, racemates and mixtures thereof, including the tautomeric compounds of Formulas 1a and 1b



Ia



Ib

The physiologically compatible salts can be formed with inorganic and organic acids, such as, for example, oxalic acid, lactic acid, citric acid, fumaric acid, acetic acid, maleic acid, tartaric acid, phosphoric acid, HCl, HBr, sulfuric acid, p-toluenesulfonic acid, methanesulfonic acid, i.a.

For salt formation of acid groups, the inorganic or organic bases are also suitable, which are known for the formation of

physiologically compatible salts, such as, for example, alkali hydroxides, such as sodium and potassium hydroxide, alkaline-earth hydroxides, such as calcium hydroxide, ammonia, amines such as ethanolamine, diethanolamine, triethanolamine, N-methylglucamine, tris-(hydroxymethyl)-methylamine, etc.

In each case, alkyl means a straight-chain or branched alkyl group, such as, e.g., methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, n-pentyl, sec-pentyl, tert-pentyl, neopentyl, n-hexyl, sec-hexyl, heptyl, or octyl.

If alkyl radical U is substituted with halogen, it can be halogenated and perhalogenated in one or more places like, for example, trifluoromethyl and trifluoroethyl.

Alkenyl and alkynyl substituents preferably contain a double bond and are in each case straight-chain or branched. For example, the following radicals can be mentioned: vinyl, 2-propenyl, 1-propenyl, 2-butenyl, 1-butenyl, 3-butenyl, 2-methyl-2-propenyl, 2-pentenyl, 4-hexenyl, ethinyl, 1-propinyl, 2-propinyl, 1-butinyl, 2-butinyl.

Cycloalkyl is defined respectively as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl. As a bicyclic compound, for example, bicycloheptane and bicyclooctane can be mentioned.

Halogen means respectively fluorine, chlorine, bromine or iodine.

Aryl is defined respectively as naphthyl or phenyl, which can be substituted by the same or a different component in one to three places.

As heteroaryl radicals, which can be bonded via the heteroatom or a carbon atom, for example, the following 5- and 6-ring heteroaromatic compounds can be mentioned:

Imidazole, indole, isooxazole, isothiazole, furan, oxadiazole, oxazole, pyrazine, pyridazine, pyrimidine, pyridine, pyrazole, pyrrole, tetrazole, thiazole, triazole, thiophene, thiadiazole, benzimidazole, benzofuran, benzoxazole, isoquinoline, quinoline. As a heteroaryl radical, 2-C_{1-6} alkyl-3-amino-1,4-benzoxazine and 2-C_{1-6}-alkyl-3-keto-1,4-benzoxazine are also suitable.

As a preferred embodiment for R^{11} in the meaning of heteroaryl, thienyl can be considered.

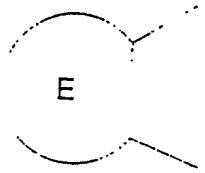
As a saturated heterocycle, for example, piperidine, pyrrolidine, morpholine, thiomorpholine, hexahydroazepine and piperazine can be mentioned. The heterocycle can be substituted in 1 to 3 places with C_{1-4} alkyl or a phenyl, benzyl or benzoyl radical that is optionally substituted with halogen. For example, there can be mentioned: N-methyl-piperazine, 2,6-dimethylmorpholine, phenylpiperazine or 4-(4-fluorobenzoyl)-piperidine.

If $-NR^8B$ or $-NR^7$-A- together with the nitrogen atom form an unsaturated heterocycle, for example, imidazole, pyrrole, pyrazole and triazole can be mentioned.

Simple substitution is preferred for substituents R^5 and R^6 in 2-position of the oxazine or thiazine, whereby substituent R^6 in particular means C_{1-6} alkyl and substituent R^5 in particular means hydrogen.

Substituent q can be linked via a C atom at any point or optionally via an N atom.

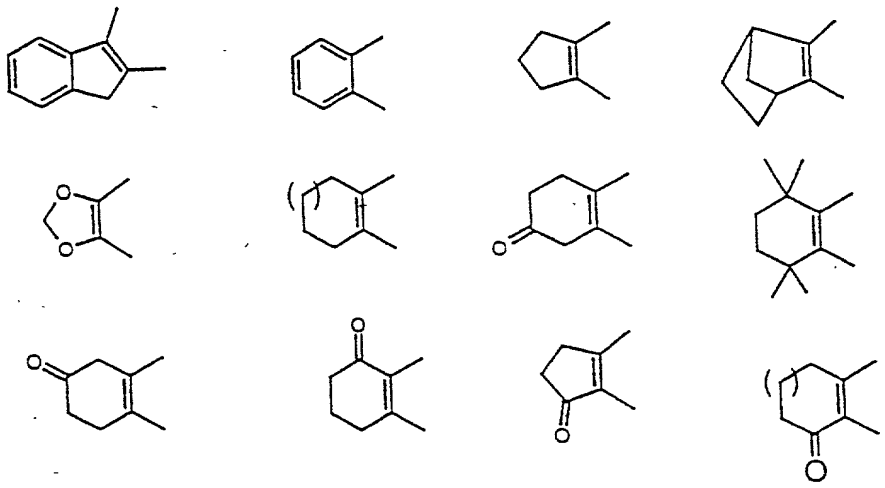
If R^1 and R^2 together with two adjacent carbon atoms form a ring, the latter can be in 5,6- or 6,7- or 7,8-position of the benzoxazine or benzothiazine and has the formula



in which

E means a saturated or unsaturated C_{3-8} alkylene radical, which is substituted in 1 to 2 places with $-(CHR^9)_r-NR^7-A-NR^8B$ and optionally in 1-2 places with C_{1-4} alkyl and in which 1 or 2 CH_2 groups can be replaced by oxygen, carbonyl or its derivative, whereby the alkylene radical can contain a slightly condensed benzene radical, such as, for example, indan, or can be present as a bicyclic compound, such as, for example, bicycloheptane.

As structures of E, there can be mentioned, for example:



As carbonyl derivatives, for example, =NOH, =N-OC_{1-6} alkyl, =NH-NH_2, =N-NH-phenyl are suitable.

Preferably, two adjacent carbon atoms of the aromatic compound are linked with C_{1-6} alkylene to a 3- to 8-membered, especially a 5- to 6-membered unsaturated ring, which is substituted in any position; in particular E means saturated or unsaturated C_{5-6} alkylene, which is substituted with $-(CHR^9)_r-NR^7-A-NR^8B$, whereby r in particular means zero.

Acyl radical R^4 is derived from straight-chain or branched aliphatic carboxylic acids, such as, for example, formic acid, acetic acid, propionic acid, butyric acid, trimethylacetic acid or caproic acid or from known benzenesulfonic acids, which can be substituted with halogen or C_{1-4} alkyl, and C_{1-4} alkanesulfonic acids, such as, for example, methanesulfonic acid, and p-toluenesulfonic acid.

Preferred embodiments of X are S and O.

In each case, R^4, R^7 and R^8 preferably mean hydrogen, and a preferred embodiment of R^3 is hydrogen.

The meaning of n preferably does not equate to zero.

Substituents R^7 and R^8 preferably mean hydrogen.

A preferred embodiment of A is especially straight-chain or branched C_{1-6} alkylene or $-(CH_2)_p-Q-(CH_2)_q-$, whereby p and q in each case especially mean 1-4.

Preferred embodiments of U are hydrogen, C_{1-6} alkyl optionally substituted with halogen, C_{3-7} cycloalkyl and phenyl, which can be substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy,

CF_3, NO_2, NH_2, $N(C_{1-4}\text{-alkyl})_2$, cyano, $CONH_2$, $-O-CH_2-O-$, $-O-(CH_2)_2-O-$, SO_2NH_2, OH, phenoxy or $COOC_{1-4}$ alkyl.

The invention also relates to the use of the compounds according to the invention for the production of a pharmaceutical agent for treating diseases, which are induced by the action of nitrogen monoxide at pathological concentrations. These include neurodegenerative diseases, inflammatory diseases, auto-immune diseases, and cardiovascular diseases.

For example, there can be mentioned:

Cerebral ischemia, hypoxia and other neurodegenerative diseases, which are brought into contact with inflammations, such as multiple sclerosis, amyotrophic lateral sclerosis and comparable sclerotic diseases, Parkinson's Disease, Huntington's Disease, Korksakoff's Disease, epilepsy, vomiting, sleep disorders, schizophrenia, depression, stress, pain, migraine, hypoglycemia, dementia, such as, e.g., Alzheimer's Disease, HIV-dementia and presenile dementia.

They are also suitable for treating diseases of the cardiovascular system and for treating auto-immune and/or inflammatory diseases, such as hypotension, ARDS (adult respiratory distress syndrome), sepsis or septic shock, rheumatoid arthritis, osteoarthritis, insulin-dependent diabetes mellitus (IDDM), inflammatory disease of the pelvis/intestine (bowel disease), meningitis, glomerulonephritis, acute and chronic liver diseases, diseases by rejection (for example allogenic heart, kidney or liver transplants) or inflammatory skin diseases such as psoriasis, etc.

Based on their profile of action, the compounds according to the invention are very well suited for inhibiting the neuronal NOS.

To use the compounds according to the invention as pharmaceutical agents, they are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient contains vehicles, adjuvants and/or additives that are suitable for enteral or parenteral administration. The administration can be done orally or sublingually as a solid in the form of capsules or tablets or as a liquid in the form of solutions, suspensions, elixirs, aerosols or emulsions or rectally in the form of suppositories or in the form of injection solutions that can also optionally be used subcutaneously, intramuscularly or intravenously, or topically in the form of aerosols or transdermal systems or intrathecally. As adjuvants for the desired pharmaceutical agent formulation, the inert organic and inorganic support media that are known to one skilled in the art are suitable, such as, e.g., water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, plant oils, polyalkylene glycols, etc. Moreover, preservatives, stabilizers, wetting agents, emulsifiers or salts for changing the osmotic pressure or buffers can optionally be contained.

For parenteral administration, especially injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are suitable.

As vehicle systems, surface-active adjuvants such as salts of bile acids or animal or plant phospholipids, but also mixtures thereof as well as liposomes or their components can also be used.

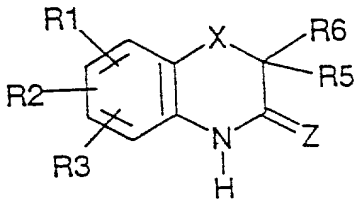
For oral administration, especially tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binders, such as, for example, lactose, corn or potato starch, are suitable. The administration can also be done in liquid form, such as, for example, as a juice, to which optionally a sweetener is added.

The dosage of the active ingredient can vary depending on method of administration, age and weight of the patient, type and severity of the disease that is to be treated and similar factors. The daily dose is 1-2000 mg, preferably 20-500 mg, whereby the dose can be given as an individual dose to be administered one time or divided into two or more daily doses.

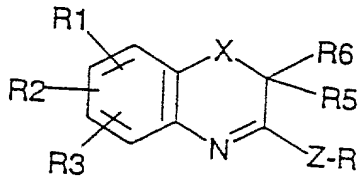
The NOS-inhibitory action of the compounds of formula I and their physiologically compatible salts can be determined according to the methods by Bredt and Snyder in Proc. Natl. Acad. Sci. USA (1989) 86, 9030-9033.

The production of the compounds according to the invention

is carried out in that a compound of formula II or its salt



IIa or



IIb

in which

R^1, R^2, R^3, R^5, R^6 and X have the above-mentioned meaning, Z is oxygen or sulfur and R means C_{1-6} alkyl, is reacted with ammonia or primary amines, whereby existing amino groups are optionally intermediately protected and optionally then acylated, the isomers are separated or the salts are formed.

The reaction with ammonia is possible under pressure in autoclaves with excess ammonia at low temperatures (-78°C) or by stirring in methanol that is saturated with ammonia at room temperature. Thiolactams are preferably reacted. If the reaction is with amines, first the iminoethers or iminothioethers are produced from lactam or thiolactam as intermediate compounds (e.g., with methyl iodide or methyl sulfate), and the latter are

reacted with or without isolation of the intermediate compounds with the corresponding amines or their salts.

As amino protective groups, for example, carbamates, such as tert-butoxycarbonyl, benzyloxycarbonyl or acetyl, are suitable.

In the precursor stages, optionally sulfides are oxidized, esters are saponified, acids are esterified, hydroxy groups are etherified or acylated, amines are acylated, alkylated, diazotized, halogenated, NO_2 is introduced or reduced, reacted with isocyanates or isothiocyanates, the isomers are separated or the salts are formed.

The saponification of an ester group can be done basically or acidically by hydrolysis being performed at room temperature or at an elevated temperature up to boiling temperature of the reaction mixture in the presence of alkali hydroxides in ethanol or other alcohols or with use of acids, such as, e.g., hydrochloric acid, and optionally salts of aminobenzoxazines or -thiazines being further processed.

The esterification of carboxylic acid is done in a way that is known in the art with diazomethane or the corresponding alcohol in acid or in the presence of an activated acid derivative. As activated acid derivatives, for example, acid chloride, -imidazolide or -anhydride are suitable.

The reduction of an ester group to alcohol is carried out in a way that is known in the art with DIBAH in suitable solvents at low temperatures. The reductive amination of a ketone or a benzaldehyde with amine while adding boron hydride provides benzylic amines. With suitably selected diamines, symmetrical or

unsymmetrical amino compounds are obtained after identical or different aldehydes are added.

In addition, a nitro group or halogen, especially bromine, can be introduced by electrophilic, aromatic substitution. Mixtures that are produced in this case can be separated in the usual way, also using HPLC. If a nitrile is present, the latter can be saponified according to known processes or can be converted into the corresponding amine, tetrazole or amidoxime, or it is in a substituted amidine by attacking substituted anilines or amines.

The Friedel-Crafts acylation is used successfully in lactams of type IIa, and then the lactam can be converted selectively into the thiolactam, or the acylation product can be reductively aminated.

The reduction of the nitro group or optionally the cyano group to the amino group is carried out catalytically in polar solvents at room temperature or at an elevated temperature under hydrogen pressure. As catalysts, metals such as Raney nickel or noble metal catalysts such as palladium or platinum optionally in the presence of barium sulfate or on vehicles are suitable. Instead of hydrogen, ammonium formate or formic acid can also be used in a known way. Reducing agents such as tin(II) chloride can also be used, such as complex metal hydrides optionally in the presence of heavy metal salts. The ester group can be advantageously introduced before the reduction as in Formula V. For nitro groups, the reduction with zinc or iron in acetic acid has proven its value.

If a single or multiple alkylation of an amino group or a CH-acid carbon position is desired, alkylation can be performed with, for example, alkyl halides according to commonly used methods. Protection of the lactam group as an anion by a second equivalent base or by a suitable protective group optionally is necessary.

The acylation of the amino group is carried out in the usual way with, for example, an acid halide or acid anhydride, optionally in the presence of a base.

The introduction of the halogens chlorine, bromine or iodine via the amino group can also be carried out, for example, according to Sandmeyer, by the diazonium salts that are formed intermediately with nitrites being reacted with Cu(I) chloride or Cu(I) bromide in the presence of the corresponding acids such as hydrochloric acid or hydrobromic acid or being reacted with potassium iodide.

Benzyl alcohols can be converted into corresponding benzyl halides as usual with methanesulfonyl chloride.

The introduction of an NO_2 group is possible by a number of known nitration methods. For example, nitration can be performed with nitrates or with nitronium tetrafluoroborate in inert solvents, such as halogenated hydrocarbons or in sulfolane or glacial acetic acid. Introduction by, e.g., nitrating acid in water or concentrated sulfuric acid as a solvent is also possible at temperatures of between -10°C and 30°C.

The isomer mixtures can be separated into enantiomers or E/Z-isomers according to commonly used methods, such as, for

example, crystallization, chromatography or salt formation. The enantiomers can also be obtained by chromatography on chiral phases as well as by stereoselective syntheses.

The production of the salts is carried out in the usual way, by a solution of the compound of Formula I -- optionally also with protected amino groups -- being mixed with the equivalent amount of acid or excess acid, which optionally is in solution, and the precipitate being separated or the solution being worked up in the usual way.

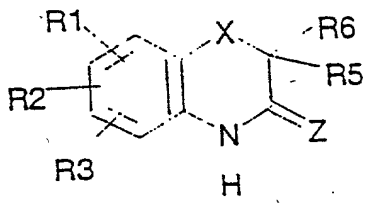
Nucleophilic substitution of benzyl halides with secondary amines yields the corresponding benzylamines.

Thiolactams of formula IIa (Z = S) are obtained from, for example, lactams with phosphorus pentasulfide (P_4S_{10}) or Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide) in suitable solvents, and compounds of Formula IIb can be obtained by, for example, reaction with Meerwein reagent (trimethyloxonium tetrafluoroborate).

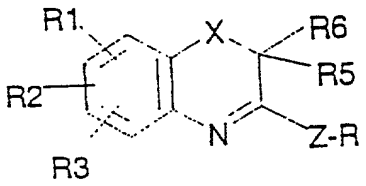
If the production of the starting compounds is not described, the latter are known and commercially available or can be produced analogously to known compounds or according to processes that are described here.

The invention also relates to the intermediate compounds of

Formulas IIa and IIb and their salts



IIa

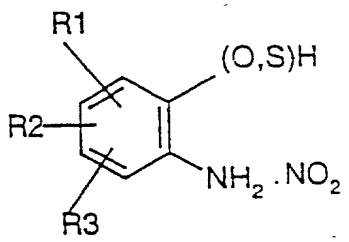


IIb

in which

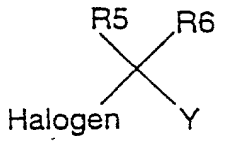
R^1, R^2, R^3, R^5, R^6 and X have the above-mentioned meaning, Z is oxygen or sulfur, and R means C_{1-6} alkyl.

The production of the compounds of Formula IIa can be done, for example, in that a compound of Formula III



III

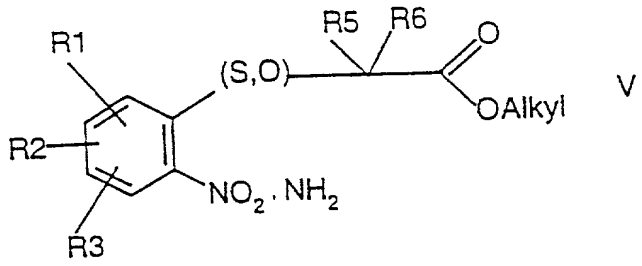
in which R^1 to R^3 have the above-mentioned meaning, is reacted with a compound of Formula IV



IV

in which R^5 and R^6 have the above-mentioned meaning, and Y is a reactive carboxyl group such as acid halide, nitrile, carboxylic acid ester, and optionally is reductively cyclized, or in that a

compound of Formula V



is reductively cyclized.

Aromatic thiols of type III are obtained, i.a., as described in Chem. Pharm. Bull. 1991, 39, 2888 and the literature that is mentioned there by rearrangement of the corresponding dimethylaminothiocarbamates.

The introduction of substituents R^1 to R^3 can be carried out in the stage of the compounds of Formula III or II.

For the production of compounds of Formula II, the aldehyde or the ketone of the corresponding 1,4-benzoxazine-3-one or 1,4-benzothiazine-3-one can be reductively aminated. This can also be done in two places with suitably selected diamines. Diamines can also be reacted with the aldehyde of 1,4-benzoxazin-3-one and simultaneously with suitably selected other aldehydes. If the introduction of a heteroaryl radical Q is desired, the corresponding halogen derivative can be substituted nucleophilically. If a primary or secondary amino group is present, it may be advantageous to protect the latter intermediately, for example by introduction of a tert-

butoxycarbonyl group, which is usually cleaved according to the amidine formation. The production of pharmacologically active compounds from the intermediate products is carried out as described above.

New compounds were identified by one or more of the following methods: melting point, mass spectroscopy, infrared spectroscopy, nuclear magnetic resonance spectroscopy (NMR). NMR spectra were measured with a Bruker 300 MHz device; the (deuterated) solvents are respectively indicated and abbreviated as follows: $CDCl_3$ (chloroform), DMSO (dimethyl sulfoxide). Alterations are indicated in delta and ppm. Here: m means multiplet, several signals; s means singlet; d means doublet; dd means double doublet, etc.; tr means triplet; q means quartet; H means hydrogen protons; J means coupling constant. In addition, THF means tetrahydrofuran, DMF means N,N-dimethylformamide, MeOH means methanol, EE means ethyl acetate, ml means milliliter, and RT means room temperature. All solvents are p.A. grade, unless otherwise indicated. All reactions are performed under protective gas, unless these are aqueous solutions.

Below, the production of several precursors, intermediate products and products is described by way of example.

Starting Compounds

A1

The synthesis of 6-formyl-2-methyl-2H-1,4-benzoxazin-3-one is described in DE-198 26 232.9, as is that of 6-formyl-2-ethyl-2H-1,4-benzoxazin-3-one and 6-formyl-2-propyl-1,4-benzoxazin-3-one.

6-((3-Aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one and 6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methylaminomethyl)-benzylaminomethyl)-2-methyl-1,4-benzoxazin-3-one

In a mixture of 4 ml of methanol and 2 ml of THF, 382 mg of 6-formyl-2-methyl-1,4-benzoxazin-3-one is dissolved and mixed with 136 mg of 3-(aminomethyl)-benzylamine. It is stirred for 30 minutes at room temperature, and then 101 mg of potassium borohydride is added. After 12 hours at room temperature, it is poured onto water, extracted three times with ethyl acetate, and the organic phase is washed with brine. It is dried with magnesium sulfate and concentrated by evaporation. 455 mg of crude product, which is provided with a protective group and then separated into individual compounds by chromatography, is obtained.

The following are produced in the same way:

6-((4-Aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one and 6-(para-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methylaminomethyl)-benzylaminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-(3-aminopropyl-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-[N-methyl-amino]-propyl-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-{[N-3-chlorobenzyl]-aminopropyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-3-chlorobenzyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-2-thienylmethyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(5-{[N-3-chlorobenzyl]-amino-n-pentyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(6-{[N-3-chlorobenzyl]-amino-n-hexyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-4-fluorobenzyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-3-trifluorobenzyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-ortho-hydroxybenzyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(5-{[N-isopropyl]-amino-n-pentyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-isopropyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-{[N-isopropyl]-amino-n-propyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-cyclopropyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-cyclopentyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-(cyclohexyl)-methyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-(cyclopropyl)-methyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-2,2,2-trifluoroethyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-4,4,4-trifluorobutyl]-amino-n-butyl}-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

Produced from 6-keto-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one are:

6-{[4-Amino-n-butyl]-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[5-amino-n-pentyl]-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{3-aminomethyl-benzylamino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[4-(N-isopropylamino)-n-butyl]-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[5-(N-isopropylamino)-n-pentyl]-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

Produced from 6-keto-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one are:

6-{[4-Amino-n-butyl]-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[5-amino-n-pentyl]-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[4-(N-isopropylamino)-n-butyl]-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[5-(N-isopropylamino)-n-pentyl]-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{3-aminomethyl-benzyl-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

From 1,3-cyclohexyl-bis-methylamine:

6-((3-Aminomethyl-cyclohex-1-yl)-methylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-on and 6-(3-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methylaminomethyl)-cyclohex-1-ylmethylaminomethyl)-2-methyl-1,4-benzoxazin-3-one

From diamines:

6-((omega-Aminobutylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((omega-aminopentylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((omega-aminohexylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

A2

6-((3-[4-Nitrobenzyl]-aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

In a mixture of 10 ml of methanol and 5 ml of THF, 573 mg of 6-formyl-2-methyl-1,4-benzoxazin-3-one is dissolved and mixed with 0.382 ml of 3-(aminomethyl)-benzylamine and 438 mg of p-nitrobenzaldehyde. It is stirred for 1 hour at room temperature, and then 173 mg of potassium borohydride is added. After 4 hours at room temperature, it is poured onto water, extracted three times with ethyl acetate, and the organic phase is washed with brine. It is dried with magnesium sulfate and concentrated by evaporation. 1.18 g of crude product, which is provided with a protective group, is obtained.

The following are produced in the same way:

6-((3-[2-Methylbenzyl]-aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((3-[2,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((3-[3-chlorobenzyl]-aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((3-[3,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

6-((3-benzylaminomethyl)-benzylaminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one

B

6-((3-[tert-Butyloxycarbonyl]aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one 1 and 6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(tert-butyloxycarbonyl)-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3-one 2

The products are obtained by reacting the mixture of 440 mg of 6-((3-amino-methyl)-benzylaminomethyl)-2-methyl-1,4-benzoxazin-3-one and 6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methylaminomethyl)-benzylaminomethyl)-2-methyl-1,4-benzoxazin-3-one in 15 ml of dichloromethane while adding 0.38 ml of triethylamine and 476 mg of di-tert-butyldicarbonate. After 12 hours at room temperature, it is diluted with dichloromethane, washed with sodium bicarbonate and then with brine. The organic phase is dried and concentrated by evaporation. After column chromatography with hexane/ethyl acetate, 160 mg of 1 and 257 mg of 2 result.

1

[1H]-NMR ($CDCl_3$): 7.27 m 1H, 6.5 to 7.18 m 7H, 5 broad 1H, 4.62 q 1H, 4.2 to 4.4 m broad 5H, 1.58 d 3H, 1.50 s 9H, 1.48 s 9H.

MS (ei) 511 m/z M+.

2

[1H]-NMR ($CDCl_3$): 7.1 to 7.3 m broad and 6.6 to 6.9 m together with 10H, 4.63 q 2H, 4.3 to 4.4 m broad 8H, 1.6 d 6H, 1.50 s 18H.

MS (ei) 630, 586, 574, 529 m/z fragments.

The following are produced in the same way:

6-((4-(**tert**-Butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one and

6-(para-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-(**tert**-Butyloxycarbonyl)-aminomethyl-cyclohex-1-yl)-methyl-(**tert**-butyloxycarbonyl)aminomethyl)-2-methyl-1,4-benzoxazin-3-one and

6-(3-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-cyclohex-1-ylmethyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((omega-(**tert**-butyloxycarbonyl)-aminobutyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((omega-(**tert**-butyloxycarbonyl)-aminopentyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((omega-(**tert**-butyloxycarbonyl)-aminohexyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-[4-nitrobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-[2-methylbenzyl]-(**tert**-butyloxycarbonyl-aminomethyl)-benzyl(**tert**-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-[2,4-dichlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-[3-chlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-[3,4-dichlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-((3-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one

6-(3-(tert-Butyloxycarbonyl)-aminopropyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-[N-methyl-(tert-butyloxycarbonyl)-amino]-propyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-aminopropyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-2-thienylmethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(5-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(6-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-hexyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-4-fluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-3-trifluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-ortho-hydroxybenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(5-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(3-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-propyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-cyclopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-cyclopentyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-(cyclohexyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-(cyclopropyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-2,2,2-trifluoroethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-(4-{[N-4,4,4-trifluorobutyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{3-(tert-butyloxycarbonyl)-aminomethyl-benzyl(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazin-3(4H)-one

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4)-one

6-{3-(tert-butyloxycarbonyl)-aminomethyl-benzyl-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazin-3(4H)-one

C

6-((3-[tert-Butyloxycarbonyl]-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazine-3(4H)-thione

192 mg of Lawesson's reagent is added at room temperature to 150 mg of 6-((3-[tert-butyloxycarbonyl]-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazin-3-one in 12 ml of dimethoxyethane, and it is stirred for 3 more hours. After concentration by evaporation and column chromatography with hexane/ethyl acetate 4:1, 140 mg of product results. The yield is 90%.

MS (ei) 527 (M+) 471, 454, 427, 415, 370, 338 m/z fragments.

The following are produced in the same way:

6-(meta-(N-[3-Thio-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(tert-butyloxycarbonyl)-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione [MS (Cl-NH_3) 719 (M+H) yield 45%] at 3 equivalents of Lawesson's reagent together with

6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(tert-butyloxycarbonyl)-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

Yield 14%.

6-((4-(**tert**-Butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(para-(N-[3-Thio-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

46% yield together with

6-(para-(N-[3-Keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-(**tert**-Butyloxycarbonyl)-aminomethyl-cyclohex-1-yl)-methyl-(**tert**-butyloxycarbonyl)aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(3-(N-[3-Thio-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-cyclohex-1-ylmethyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((omega-(**tert**-Butyloxycarbonyl)-aminobutyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((omega-(**tert**-butyloxycarbonyl)-aminopentyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-1,4-benzoxazine-3(4H)-thione

6-((omega-(**tert**-butyloxycarbonyl)-aminohexyl-(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-[4-nitrobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-[2-methylbenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-[2,4-dichlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-[3-chlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-[3,4-dichlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-((3-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(3-(tert-Butyloxycarbonyl)-aminopropyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(3-[N-methyl-(tert-butyloxycarbonyl)-amino]-propyl-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(3-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-aminopropyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-2-thienylmethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(5-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(6-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-hexyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-4-fluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-3-trifluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-ortho-hydroxybenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(5-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(3-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-propyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-cyclopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-cyclopentyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-(aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-(cyclohexyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

(6-(4-{[N-(cyclopropyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-2,2,2-trifluoroethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-(4-{[N-4,4,4-trifluorobutyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazine-3(4H)-thione

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazine-3(4H)-thione

6-{3-(tert-butyloxycarbonyl))-aminomethyl-benzyl(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazine-3(4H)-thione

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazine-3(4H)-thione

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-2-methyl-2H-naphth[2,3-b]-1,4-oxazine-3(4H)-thione

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

6-{3-(tert-butyloxycarbonyl)-aminomethyl-benzyl-(tert-butyloxycarbonyl)-amino}-6,7-trimethylene-2-methyl-2H-1,4-benzoxazine-3(4H)-thione

Example 1

6-((3-[tert-Butyloxycarbonyl]-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-1,4-benzoxazine

140 mg of 6-((3-[tert-butyloxycarbonyl]-aminomethyl)-benzyl-(tert-butyloxy-carbonyl)-aminomethyl)-2-methyl-1,4-benzoxazine-3-thione is stirred in 50 ml of saturated ammonia solution in methanol (commercially available). After 1 day at room temperature, the crude product is obtained after concentration by evaporation. Column chromatography with ethyl acetate purifies the product. A 75% yield results.

[1H]-NMR (DMSO): 7.30 dd 2H, 7.14 dd 2H, 7.08 d 1H, 6.6 to 6.75 m 4H including amidine NH, 4.62 q 1H, 4.35 s broad 2H, 4.22 s broad 2H, 4.15 s broad 2H, 1.42 s 9H, 1.40 s 9H, 1.28 d 3H.

MS (ei): 510 m/z (M+).

The following are produced in the same way:

6-(meta-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(tert-butyloxycarbonyl)-aminomethyl)-benzyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

95% yield.

[1H]-NMR (DMSO): 7.30 dd 1H, 7.10 m 3H, 6.6 to 6.75 m 10H including amidine NH, 4.64 q 2H, 4.30 s broad 4H, 4.21 s broad 4H, 1.42 s 18H, 1.29 d 6H.

MS (Cl-NH_3) 685 m/z (M+1)

6-(meta-(N-[3-Keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

90% yield

MS (Cl-NH_3) 686 m/z (M+1)

6-((4-(**tert**-Butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(para-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

92%, [1H]-NMR (DMSO): 7.17 s 2H, 6.6 to 6.75 m 8H, 4.64 q 2H, 4.30 s broad 4H, 4.21 s broad 4H, 1.41 s 18H, 1.28 d 6H.

MS (Cl-thioglycerol) 685 m/z (M+1)

6-(para-(N-[3-Keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

(6-((3-(**tert**-Butyloxycarbonyl)-aminomethyl-cyclohex-1-yl)-methyl-(**tert**-butyloxycarbonyl)aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

MS (Cl-thioglycerol) 517 m/z (M+1)

6-(3-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-(tert-butyloxycarbonyl)-aminomethyl)-cyclohex-1-ylmethyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((omega-(tert-butyloxycarbonyl)-aminobutyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((omega-(tert-butyloxycarbonyl)-aminopentyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((omega-(tert-butyloxycarbonyl)-aminohexyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-[4-nitrobenzyl]-(tert-butyloxycarbonyl)-aminomethyl)-benzyl(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-[2-methylbenzyl]-(tert-butyloxycarbonyl)-aminomethyl)-benzyl(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-[2,4-dichlorobenzyl]-(tert-butyloxycarbonyl)-aminomethyl)-benzyl(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-[3-chlorobenzyl]-(tert-butyloxycarbonyl)-aminomethyl)-benzyl(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-[3,4-dichlorobenzyl]-(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-((3-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-benzyl(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(3-(tert-Butyloxycarbonyl)-aminopropyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(3-[N-methyl-(tert-butyloxycarbonyl)-amino]-propyl-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(3-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-aminopropyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-2-thienylmethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(5-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(6-{[N-3-chlorobenzyl]-(tert-butyloxycarbonyl)-amino-n-hexyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-4-fluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-3-trifluorobenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-ortho-hydroxybenzyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(5-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-pentyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(3-{[N-isopropyl]-(tert-butyloxycarbonyl)-amino-n-propyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-cyclopropyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl}-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-cyclopentyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-(cyclohexyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-(cyclopropyl)-methyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-2,2,2-trifluoroethyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-(4-{[N-4,4,4-trifluorobutyl]-(tert-butyloxycarbonyl)-amino-n-butyl}-(tert-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine

6-{3-(tert-butyloxycarbonyl)-aminomethyl-benzyl(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine

6-{[4-(tert-butyloxycarbonyl)-amino-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine

6-{[5-(tert-butyloxycarbonyl)-amino-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine

6-{[4-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-butyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine

6-{[5-(N-isopropyl(tert-butyloxycarbonyl)-amino)-n-pentyl]-(tert-butyloxycarbonyl)-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine

6-{3-(tert-butyloxycarbonyl)-aminomethyl-benzyl-(tert-butyloxycarbonyl)-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine

Example 2

6-((3-Aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

95 mg of 6-((3-[**tert**-butyloxycarbonyl]-aminomethyl)-benzyl-(**tert**-butyloxycarbonyl)-aminomethyl)-3-amino-2-methyl-1,4-benzoxazine is stirred into 3 ml of dioxane with 2 ml of 4N hydrochloric acid (solution in dioxane). After 12 hours, it is diluted with some ethyl acetate, the crystals are suctioned off, washed with a little ethyl acetate and dried in a vacuum. 66 mg of product (92% yield) is obtained.

[1H]-NMR (DMSO): 9.9 broad, 9.5 broad, 8.5 broad s, 7.37 to 7.70 m 6 H, 7.11 d 1H, 5.36 q 1H, 4.15 broad 2H, 4.14 broad 2H, 4.04 broad 2H, 1.50 d 3H.

The following are produced in the same way:

6-(meta-(N-[3-Keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

Yield 99%

[1H]-NMR (DMSO): 9.9 broad, 9.7 broad, 7.0 to 7.75 m 10H, 5.33 q 1H, 4.70 q 1H, 4.15 broad 4H, 4.1 m 4H, 1.50 d 3H, 1.44 d 3H.

6-(meta-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride (HCl content not determined)

Yield 87%.

[1H]-NMR (DMSO): 9.9 broad, 9.5 broad, 7.38 dd 2H, 7.5 m 3H, 7.65 dd 2H, 7.75 s 1H, 7.11 d 2H, 5.33 q 2H, 4.15 broad 8H, 1.50 d 6H.

6-((4-Aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-1,4-benzoxazine trihydrochloride

6-(para-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride (HCl content is not determined)

[1H]-NMR (DMSO): 9.9 broad, 9.5 broad, 7.64 s 4H, 7.48 dd 2H, 7.35 dd 2H, 7.12 d 2H, 5.33 q 2H, 4.19 broad 4H, 4.11 broad 4H, 1.50 d 6H.

6-(para-(N-[3-Keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-aminomethyl-cyclohex-1-yl)-methyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9.4 broad, 8.1 broad s, 7.5 d 1H, 7.43 d 1H, 7.12 d 1H, 5.34 q 1H, 4.12 broad 2H, 1.2 to 2.9 m 14 H, 1.51 d 3H.

6-(3-(N-[3-Amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-cyclohex-1-ylmethyl-aminomethyl)-3-amino-2-methyl-1,4-benzoxazine trihydrochloride (HCL content is not determined)

6-((omega-Aminobutyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((omega-aminopentyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

Yield 84%

[1H]-NMR (DMSO): 13.2 broad, 10.1 broad, 9.0 broad, 7.48 d 1H, 7.37 d 1H, 7.13 d 1H, 5.34 q 1H, 4.10 broad 2H, 2.7 to 2.9 m 4H, 0.85 to 1.78 m 6H, 1.50 d 3H.

6-((omega-Aminohexyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[4-nitrobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO); 9.9 broad, 8.28 d 2H, 7.92 d 2H, 7.77 s 1H, 7.65 d 2H, 7.5 m 2H, 7.39 m 1H, 7.11 d 1H, 5.34 q 1H, 4.35 broad s 2H, 4.21 s 2H, 4.16 s 4H, 1.51 d 3H.

6-((3-[2-Methylbenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[2,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[3-chlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[3,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-benzylaminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(3-Aminopropyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(3-[N-methylamino]-propyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9-10 m broad NH, 7.49 d 1H, 7.40 dd 1H, 7.12 d 1H, 5.39 q 1H, 4.11 d 2H, 2.5 s 3H, 3.05 m 4H, 2.12 m 2H, 1.51 d 3H.

<u>6-(3-{[N-3-Chlorobenzyl]-aminopropyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.6 m broad, 7.74 s 1H, 7.57 dd 1H, 7.49 d 3H, 7.39 d 1H, 7.12 d 1H, 5.35 q 1H, 4.15 s 2H, 4.10 s broad 2H, 3.05 m 4H, 2.15 m 2H, 1.49 d 3H.

<u>6-(4-{[N-3-Chlorobenzyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 7.75 s 1H, 7.57 dd 1H, 7.49 m 3H, 7.39 dd 1H, 7.12 d 1H, 5.37 q 1H, 4.10 d broad 4H, 2.9 m 4H, 1.74 m 4H, 1.49 d 3H.

<u>6-(4-{[N-2-Thienylmethyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 7.63 d 1H, 7.47 s 1H, 7.38 dd 2H, 7.1 m 2H, 5.34 q 1H, 4.35 s broad 2H, 4.09 s broad 2H, 2.9 m 4H, 1.75 m 4H, 1.50 d 3H.

<u>6-(5-{[N-3-Chlorobenzyl]-amino-n-pentyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 7.74 s 1H, 7.56 dd 1H, 7.47 m 3H, 7.38 dd 1H, 7.11 d 1H, 5.35 q 1H, 4.15 d 2H, 4.09 d 2H, 2.9 m 4H, 1.72 m 4H, 1.51 d 3H, 1.4 m 2H.

<u>6-(6-{[N-3-Chlorobenzyl]-amino-n-hexyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

6-(4-{[N-4-Fluorobenzyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9.5 m broad, 7.67 m 2H, 7.48 s 1H, 7.39 dd 1H, 7.29 dd 2H, 7.12 d 1H, 5.37 q 1H, 4.1 m 4H, 2.9 m 4H, 1.75 m 4H, 1.50 d 3H.

6-(4-{[N-3-Trifluorobenzyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9.6 m broad, (8.05 s, 7.93 d, 7.8 d, 7.7 dd, 7.47 s, 7.39 d, 7.13 d, in each case 1H), 5.36 q 1H, 4.25 broad 2H, 4.10 broad 2H, 2.9 m 4H, 1.78 m 4H, 1.50 d 3H.

6-(4-{[N-ortho-Hydroxybenzyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(5-{[N-isopropyl]-amino-n-pentyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9.5 m broad, 9.9 m broad NH, 7.49 d 1H, 7.39 dd 1H, 7.13 d 1H, 5.37 q 1H, 4.10 s 2H, 3.2 hept 1H, 2.85 m 4H, 1.7 m 4H, 1.4 m 2H, 1.51 d 3H, 1.26 d 6H.

6-(4-{[N-Isopropyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR (DMSO): 9.5 m broad, 9 m broad NH, 7.48 d 1H, 7.39 dd 1H, 7.12 d 1H, 5.35 q 1H, 4.11 s 2H, 3.25 hept 1H, 2.9 m 4H, 1.75 m 4H, 1.5 d 3H, 1.27 d 6H.

<u>6-(3-{[N-Isopropyl]-amino-n-propyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 9.1 m broad NH, 7.49 d 1H, 7.4 dd 1H, 7.12 d 1H, 5.35 q 1H, 4.11 s 2H, 3.3 hept 1H, 3.0 m 4H, 2.1 m 2H, 1.5 d 3H, 1.27 d 6H.

<u>6-(4-{[N-Cyclopropyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

<u>6-(4-{[N-cyclopentyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 9.1 m broad NH, 7.48 d 1H, 7.39 dd 1H, 7.12 d 1H, 5.37 q 1H, 4.09 s 2H, 2.9 m 4H, 1.95 m 2H, 1.7 m 8H, 1.50 d 3H, 1.52 m 1H.

<u>6-(4-{[N-(Cyclohexyl)-methyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9-10 m broad NH, 7.49 d 1H, 7.39 dd 1H, 7.12 d 1H, 5.37 q 1H, 4.10 d 2H, 2.91 m 4H, 2.74 m 2H, 1.85 to 1.6 m 10H, 1.50 d 3H, 1.3 to 0.85 m 5H.

<u>6-(4-{[N-(Cyclopropyl)-methyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

<u>6-(4-{[N-2,2,2-Trifluoroethyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride</u>

[1H]-NMR (DMSO): 9.5 m broad, 7.49 d 1H, 7.39 dd 1H, 7.11 d 1H, 5.37 q 1H, 4.1 s 2H, 3.99 m 2H (CH_2CF_3), 3.02 m 2H, 2.92 m 2H, 1.75 m 4H, 1.50 d 3H.

6-(4-{[N-4,4,4-Trifluorobutyl]-amino-n-butyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-{[4-Amino-n-butyl]-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine trihydrochloride

6-{[5-amino-n-pentyl]-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine trihydrochloride

6-{[3-Aminomethyl]-benzylamino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine trihydrochloride

[1H]-NMR (DMSO): 9.5 to 8.5 m broad, 7.9 s 1H, 7.8 d 1H, 7.64 d 1H, 7.53 m 2H, 7.0 s 1H, 5.41 q 1H, 4.5 m 1H, 4.3 s 2H, 4.1 s 2H, 2.9 m 2H, 2.3 m 1H, 2.1 m 2H, 1.8 m 1H, 1.55 d 3H.

6-{[4-(N-Isopropylamino)-n-butyl]-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine trihydrochloride

6-{[5-(N-isopropylamino)-n-pentyl]-amino}-6,7,8,9-tetrahydro-3-amino-2-methyl-2H-naphth[2,3-b]-1,4-oxazine trihydrochloride

[1H]-NMR(MeOH): 7.34 s 1H, 6.85 s 1H, 5.13 q 1H, 4.4 m 1H, 3.29 m 1H, 3.05 dtr 2H, 2.92 m 2H, 2.8 m 2H, 2.15 m 1H, 2.0 m 1H, 1.8 m 2H, 1.7 m 2H, 1.6 m 2H, 1.47 d 3H, 1.24 d 6H.

6-{[4-Amino-n-butyl]-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-{[5-amino-n-pentyl]-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-{[4-(N-isopropylamino)-n-butyl]-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

[1H]-NMR(MeOH): 7.51 s 1H, 7.0 s 1H, 5.13 q 1H, 4.7 m 1H, 3.3 m 1H, 3.1 m 2H, 3.0 m 2H, 2.9 m 2H, 2.5 m 1H, 2.2 m 1H, 1.8 m 2H, 1.7 m 2H, 1.49 d 3H, 1.27 d 6H.

6-{[5-(N-Isopropylamino)-n-pentyl]-amino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-{[3-aminomethyl]-benzylamino}-6,7-trimethylen-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

The following are obtained according to commonly used methods:

6-(5-{[N-Isopropyl]-amino-n-pentyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine succinate [Stoichiometry 1-1.5 times]

Flash point: 119.4°C

6-(5-{[N-Isopropyl]-amino-n-pentyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trispropionate

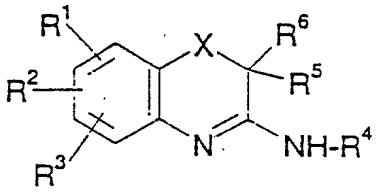
Flash point: 134.9°C

6-(5-{[N-Isopropyl]-amino-n-pentyl}-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine oxalate [Stoichiometry 1-1.5 times]

Flash point: 215.2°C

Claims

1. Compounds of Formula I, their tautomeric and isomeric forms and salts



(I)

in which

X is O, SO_m or Se,

R^1 is $-(CHR^9)_n-NR^7-A-NR^8-B$,

R^2 is hydrogen or

R^1 and R^2 together with two adjacent carbon atoms form a 5-, 6-, 7- or 8-membered ring, which is monocyclic or bicyclic, saturated or unsaturated and in which 1 or 2 CH_2 groups can be replaced by oxygen or carbonyl, and which is substituted with $(CHR^9)_r-NR^7-A-NR^8-B$, and can be substituted with C_{1-4} alkyl,

R^3 means hydrogen, halogen, NO_2, cyano, CF_3, $-OCF_3$, $-S-R^9$, $-O-R^9$, C_{3-7} cycloalkyl, $-NR^9-C(=NR^{10})-R^{11}$, $-NH-CS-NR^{12}R^{13}$, $-NH-CO-NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-CO-NR^{12}R^{13}$, $-CO-R^{14}$, $NR^{15}R^{16}$, C_{6-10} aryl, which optionally is substituted with halogen, cyano, C_{1-4} alkyl, $-S-R^9$, or $-O-R^9$,

5- or 6-membered heteroaryl with 1 to 4 oxygen, sulfur or nitrogen atoms,

C_{1-6} alkyl, which optionally is substituted with halogen, $-OR^9$, $-SR^9$, $-NR^{12}R^{13}$, $=NR^{12}$, $=NOC_{1-6}$ alkyl, =N-NHaryl, phenyl, C_{3-7} cycloalkyl or 5- or 6-membered heteroaryl,

C_{2-6} alkenyl, which optionally is substituted with halogen, $CONH_2$, C≡N or phenyl,

C_{2-6} alkinyl, which optionally is substituted with halogen, $CONH_2$, C≡N or phenyl,

R^4 means hydrogen or acyl,

R^5 and R^6, independently of one another, mean hydrogen, C_{3-7} cycloalkyl, phenyl, C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl radicals, which can be substituted in each case with halogen, OH, $O-C_{1-6}$ alkyl, SH, $S-C_{1-6}$ alkyl, $NR^{15}R^{16}$, 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, phenyl or C_{3-7} cycloalkyl,

R^7 means hydrogen, C_{1-6} alkyl, which can be substituted with phenyl, $COOC_{1-6}$ alkyl or $CO-C_{1-6}$ alkyl,

R^8 means hydrogen, C_{1-6} alkyl, which can be substituted with phenyl, $COOC_{1-6}$ alkyl or COC_{1-6} alkyl,

A means straight-chain or branched C_{1-6} alkylene, straight-chain or branched C_{1-6} alkenylene or $-(CH_2)_p-Q-(CH_2)_q-$,

B means hydrogen or $-(CH_2)_p-U$,

Q means C_{3-7} cycloalkyl, indanyl, 5-, 6- or 7-membered saturated heterocycloalkyl with 1-2 N, O or S atoms,

C_6-C_{10} aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which can be anellated with benzene,

U means hydrogen, C_{1-6} alkyl optionally substituted with halogen, C_{3-7} cycloalkyl, indanyl, C_{7-10} bicycloalkyl, C_{6-10} aryl or 5- or 6-membered heteroaryl with 1-3 N, O or S atoms, which can be anellated with benzene, whereby the aryl and heteroaryl radical can be substituted with halogen, C_{1-4} alkyl, C_{1-4} alkoxy, CF_3, NO_2, NH_2, $N(C_{1-4}$ alkyl$)_2$, cyano, $CONH_2$, $-O-CH_2-O-$, $-O-(CH_2)_2-O-$, SO_2NH_2, OH, phenoxy or $COOC_{1-4}$ alkyl,

or

R^8 and B together with the nitrogen atom form a 5- to 7-membered saturated heterocycle, which can contain another oxygen, nitrogen or sulfur atom and can be substituted with C_{1-4} alkyl, phenyl, benzyl or benzoyl or form an unsaturated 5-membered heterocycle, which can contain 1-3 N atoms and can be substituted with phenyl, C_{1-4} alkyl or halogen, or

R^7 and A together with the nitrogen atom form a 5- to 7-membered saturated heterocycle, which can contain another oxygen, nitrogen or sulfur atom or forms an unsaturated 5-membered heterocycle, which can contain 1-3 N atoms,

m means 0, 1 or 2,

n and r mean 0, 1 to 6,

p and q mean 0 to 6,

R^9 and R^{10} mean hydrogen or C_{1-6} alkyl,

R^{11} means C_{1-6} alkyl, $-NH_2$, $-NH-CH_3$, $-NH-CN$, C_{6-10} aryl optionally substituted with halogen, C_{1-4} alkyl or CF_3, or 5- or 6-membered heteroaryl with 1 to 4 nitrogen, sulfur or oxygen atoms that is optionally substituted with halogen, C_{1-4} alkyl or CF_3,

R^{12} and R^{13} mean hydrogen, C_{1-6} alkyl, phenyl optionally substituted with halogen or C_{1-4} alkyl, benzyl optionally substituted with halogen or C_{1-4} alkyl, or C_{3-7} cycloalkyl,

R^{14} means hydrogen, hydroxy, C_{1-6} alkoxy, phenyl, C_{1-6} alkyl optionally substituted with CO_2H, CO_2C_{1-6} alkyl, hydroxy, C_{1-4} alkoxy, halogen, $NR^{15}R^{16}$, $CONR^{12}R^{13}$, or phenyl, or C_{2-6} alkenyl optionally substituted with phenyl, cyano, $CONR^{12}R^{13}$ or CO_2C_{1-4} alkyl,

R^{15} and R^{16} mean hydrogen, C_{1-6} alkyl, phenyl or benzyl or

R^{15} and R^{16} together with the nitrogen atom form a saturated 5-, 6-, or 7-membered ring, which can contain another nitrogen, oxygen or sulfur atom and can be substituted with C_{1-4} alkyl, phenyl, benzyl or benzoyl,

whereby

if X = 0, R^6 means methyl and R^2, R^3, R^4 and R^5 mean hydrogen, R^1 is not 6-((4-aminobenzyl)aminomethyl), 6-((4-dimethylaminobenzyl)aminomethyl), 6-((4-aminobenzyl)(tert-butyloxycarbonyl)aminomethyl), or 6-((4-dimethylaminobenzyl)(tert-butyloxycarbonyl)aminomethyl).

2. Compounds according to claim 1, in which R^5 is hydrogen.

3. Compounds according to claims 1-2, in which R^6 is C_{1-6} alkyl.

4. Compounds according to claims 1-3, in which R^4 is hydrogen.

5. Compounds according to claims 1-4, in which X is oxygen or sulfur.

6. Compounds according to claims 1-5, in which R^1 and R^2 together with two adjacent carbon atoms mean a 3- to 8-membered, preferably 5- to 6-membered ring, which is substituted with $-(CHR^9)_r-NR^7-A-NR^8B$.

7. Compounds according to claim 6, in which r = 0.

8. Compounds according to claims 1-7, in which A means a straight-chain or branched C_{1-6} alkylene or $-(CH_2)_p-Q-(CH_2)_q-$, and p and q mean 1-4.

9. Compounds according to claim 1, in which U means hydrogen, alkyl that is optionally substituted with halogen, C_{3-7} cycloalkyl and optionally substituted phenyl.

10. 6-((3-Aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(meta-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(meta-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((4-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(para-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(para-(N-[3-keto-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-benzyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-aminomethyl-cyclohex-1-yl)-methyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-(3-(N-[3-amino-2-methyl-2H-1,4-benzoxazin-6-yl]-methyl-aminomethyl)-cyclohex-1-ylmethyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((omega-aminobutyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((omega-aminopentyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((omega-aminohexyl-aminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[4-nitrobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[2-methylbenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[2,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[3-chlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

6-((3-[3,4-dichlorobenzyl]-aminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride

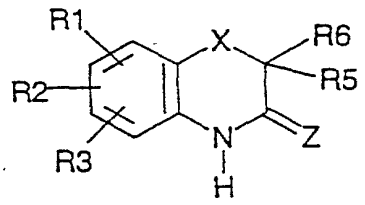
6-((3-benzylaminomethyl)-benzylaminomethyl)-3-amino-2-methyl-2H-1,4-benzoxazine trihydrochloride
according to claim 1.

11. Pharmaceutical agent that contains a compound according to claims 1-10 and one or more pharmaceutically common vehicles or adjuvants.

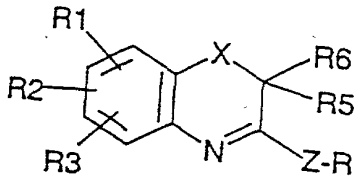
12. Use of a compound according to claims 1-10 for the production of a pharmaceutical agent for treating a disease that is triggered by NOS.

13. Use according to claim 11 for treatment of neurodegenerative diseases.

14. Process for the production of a compound of formula I according to claims 1-3, characterized in that a compound of formula II or its salt



IIa or

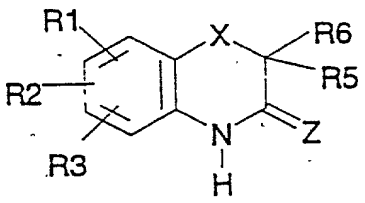


IIb

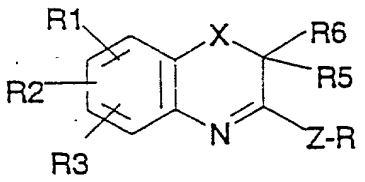
in which

R^1, R^2, R^3, R^5, R^6 and X have the above-mentioned meaning, Z is oxygen or sulfur and R means C_{1-6} alkyl, is reacted with ammonia or primary amines, whereby existing amino groups are optionally intermediately protected and optionally then acylated, the isomers are separated or the salts are formed.

15. Compounds of formulas IIa and IIb



IIa



IIb

in which

R^1, R^2, R^3, R^5, R^6 and X have the above meaning, X is oxygen or sulfur, and R means C_{1-6} alkyl.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

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Additional joint inventors are named on separately numbered sheets attached hereto.

DECLARATION FOR PATENT APPLICATION

51627A

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

BENZOXAZINE AND BENZOTHIAZINE DERIVATIVES AND THEIR USE IN MEDICINES

the specification of which

- ☐ is attached hereto
- ■ was filed on 16 SEPTEMBER 1999 as United States Application Number or PCT International Application Number PCT/EP99/07089 and (if applicable) was amended on _____

I hereby authorize our attorneys to insert the serial number assigned to this application.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35 U.S C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 USC §119			
APPLICATION NO.	COUNTRY	DAY/MONTH/YEAR FILED	PRIORITY CLAIMED
198 44 291.2	GERMANY	18/09/1998	YES

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)	
APPLICATION NUMBER	FILING DATE

I hereby claim the benefit under 35 U S.C §120 of any United States application, or §365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1 56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

PRIOR U.S./PCT INTERNATIONAL APPLICATION(S) DESIGNATED FOR BENEFIT UNDER 37 U.S.C. §120		
APPLICATION NO.	FILING DATE	STATUS — PATENTED, PENDING, ABANDONED

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith: I. William Millen (19,544); John L. White (17,746); Anthony J. Zelano (27,969); Alan E.J. Branigan (20,565); John R. Moses (24,983); Harry B. Shubin (32,004); Brion P. Heaney (32,542); Richard J. Traverso (30,595), John A. Sopp (33,103); Richard M. Lebovitz (37,067); John H. Thomas (33,460); Catherine M. Joyce (40,668); Nancy J. Axelrod (44,014); James T. Moore (35,619); James E. Ruland (40,921) and Jennifer J Branigan (37,432)

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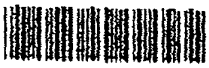

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